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TRANSMITTAL FORM

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Total Number of Pages in This Submission: 4

Application Number	09/881,326
Filing Date	06/14/2001
First Named Inventor	David Rozema
Group Art Unit	1636
Examiner Name	William Sandals
Attorney Docket Number	Mirus.013.04.02

ENCLOSURES *(check all that apply)*

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) *(please identify below)*:

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Remarks

Attached is a signed copy of the originally faxed Supplement.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Mirus Corporation
Signature	M K Johnson
Date	01/20/2003

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being sent by facsimile transmission to art unit 1636, 703.308.4242, and addressed to: Commissioner for Patents, Washington, DC 20231 on this date: 01/20/2003

Typed or printed name	Mark K. Johnson		
Signature	M K Johnson	Date	01/20/2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Jon A. Wolff, James E. Hagstrom, Sean D. Monahan, Paul M. Slattum, David B. Rozema and Vladimir G. Budker**	)	
Serial No.: **09/881,326**	)	
,Filed: **06/14/2001**	)	Examiner: **William Sandals**
Group Art Unit: **1636**	)	

For: **Intravascular Delivery of Non-Viral Nucleic Acid**

SUPPLEMENTAL INFORMATION

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants have attached information that they believe is pertinent to the examination of this case. In particular, the information has been copied from the file history of the U.S. Patent No. 5,698,531 issued to Nabel *et al.* which is the primary prior art cited in Applicants' case.

Applicants wish to supplement their argument that the '531 patent does not teach transfection of extravascular parenchymal cells. The information provided also supplements the telephone interview held on Thursday, January 16, 2003 between Applicants and the Examiner where Applicants call attention to an article reviewing the state of gene delivery published by Elizabeth Nabel (Circulation. 1995;91:541-548.). Elizabeth Nabel states on page 544, 1st column, last paragraph:

> "Several observations concerning the delivery of recombinant genes and patterns of gene expression can be drawn from these studies. Infusion of vector into normal arteries with an intact endothelium results in transfection of intimal cells (primarily endothelial cells). [at this point, Ms. Nabel cites her own work among others published well after the filing date of the '531 patent.] Injury to the vessel and/or application of pressure to the vector infusate results in delivery of DNA transmurally and gene expression in the media".

This paragraph dictates the overall extent of transfection into blood vessels in 1995 as well as the '531 inventors' ability to 'teach' the art in years prior to 1995: 1) transfection

into intimal cells (1st layer of vasculature without injury; and 2) transfection into medial cells (2nd layer of vasculature) with injury.

As further evidence of the '531 inventors' lack of ability to teach Applicants' delivery methods, Applicants call the Examiner's attention to the file history of the '531 patent. In the amendment filed on November 22, 1993, page 3, the inventors limit their teachings to "site-specifically transforming cells." On page 5 site-specificity is limited to "using physical methods to place the DNA or RNA sequences at specific locations." On page 10 of the '531 amendment, the inventors provide data to show delivery to vessel cells and lack of delivery to extravascular cells by ß-galactosidase activity: "In addition, no ß-galactosidase activity was observed in random microscopic segments from the liver, lung, or kidney, except for cells with endogenous activity."

Importantly, on page 19 of the same amendment, the '531 inventors attempt to differentiate their process from a prior art process and thereby limit their '531 teachings to a physical method of delivery (injury to the endothelial wall): 'Firstly, Myers [prior art to Nabel *et al.*] differs from the present invention in that it uses the vector as a homing beacon to ensure that the DNA sequence reaches the appropriate cell. In contrast, the present invention uses physical methods to deliver recombinant genes to specific lesions *in vivo* and differs from Myers targetable injectable vector." Applicants point out that in the '531 inventors' own language they state that they must deliver to "specific lesions" which are caused by their denuding processes and differs from an injectable vector.

In a further limitation to the '531 teachings, Paper 19, an Office Action to the '531 inventors, states on page 2: "Clearly a syringe, as would be used for injection purposes, would be materially distinct from the balloon catheter". In Paper 26, an examiner interview summary record attempts to convince Nabel *et al.* to "reduce issues of prior art" by limiting their claims to a balloon catheter, stating: "Examiner suggested bringing out balloon catheter concept in the method claims." Nabel *et al.* respond and finally limit their claims to a catheter.

By their own statements, the inventors of the '531 patent have limited their teachings to physical denuding of vessel walls followed by physical delivery to specific locations of a vessel wall. One would have to ignore logic to conclude that the '531 patent teaches non-local delivery of genetic material to extravascular parenchymal cells by injection as taught by Applicants.

Applicants request that the Examiner contact them regarding this correspondence after his consideration.

Respectfully submitted,

Mark K. Johnson Reg. No. 35,909
Mirus
505 South Rosa Road
Madison, WI 53719
608.238.4400

I hereby certify that this correspondence is being sent by facsimile transmission to art unit 1636, 703.308.4242: Commissioner for Patents, Washington, DC on Thursday, January 16, 2003.

Signature